In the Claims

1-12 (cancelled)

13. (original) A method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, wherein said donor heteromeric variable region comprises three light chain donor CDRs and three heavy chain donor CDRs, and wherein said method comprises;

a) providing;

i) a first oligonucleotide encoding an altered light chain variable region, wherein said altered light chain variable region comprises:

A) four unvaried human germline light chain framework regions, wherein three of said four unvaried human germline light chain framework regions are from a human kappa light chain gene selected from the group consisting of: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8; and

B) three light chain altered variable region CDRs, wherein at least one of said three light chain altered variable region CDRs is a light chain donor CDR variant, and wherein said light chain donor CDR variant comprises a different amino acid at only one, two, three or four positions compared to one of said three light chain donor CDRs, and

ii) a second oligonucleotide encoding an altered heavy chain variable region, wherein said altered heavy chain variable region comprises;

A) four unvaried human germline heavy chain framework regions, wherein three of the four unvaried human germline heavy chain framework regions are from a human heavy chain gene selected from the group consisting of: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VHI-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51; and

B) three heavy chain altered variable region CDRs, wherein at least one of said three heavy chain altered variable region CDRs is a heavy chain donor CDR variant, and wherein said heavy chain donor CDR variant comprises a different amino acid at only one, two, three, or four positions compared to one of said heavy chain donor CDRs, and

b) expressing said first and second oligonucleotides under conditions such that a heteromeric variable region binding fragment is generated that exhibits higher antigen binding affinity than said donor heteromeric variable region.

14. (original) The method of Claim 13, wherein said expressing is coexpressing.

15. (original)The method of Claim 13, wherein said higher antigen binding affinity is at least 2-fold higher than the affinity of said donor heteromeric variable region.

16. (original)The method of Claim 13, wherein said higher antigen binding affinity is at least 3-fold higher than the affinity of said donor heteromeric variable region.

17. (currently amended) A method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, wherein said donor heteromeric variable region comprises three light chain donor CDRs and three heavy chain donor CDRs, said method comprising;

a) providing;

i) a first population of ~~first~~ oligonucleotides encoding four unvaried human germline light chain framework regions, wherein three of said four unvaried human germline light chain framework regions are from a human kappa light chain gene selected from the group consisting of: A11, A17, A18, Al9, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8;

ii) a second population of ~~second~~ oligonucleotides encoding:

A) three light chain CDRs, wherein the three light chain CDRs comprise at least one light chain CDR altered with respect to said light chain donor CDRs~~, first light chain CDRs, wherein said first light chain CDRs comprise donor CDR variants, wherein said donor CDR variants comprise a different amino acid at only one, two, three or four positions compared to one of said three light chain donor CDRs~~,

~~B) second light chain CDRs, wherein said second light chain CDRs encode each of said three light chain donor CDRs~~;

iii) wherein said first population of oligonucleotides and said second population of oligonucleotides overlap to encode a population of light chain variable regions comprising said unvaried human germline light chain framework regions and said light chain CDRs,

~~iii)~~ iv) a third population of ~~third~~ oligonucleotides encoding four unvaried human germline heavy chain framework regions, wherein three of the four unvaried human germline heavy chain framework regions are from a human heavy chain gene selected from the group consisting of: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH-46, VH3-9, VH3- 66, VH3-

74, VH4-31, VH-18, VH1-69, VH-3-7, VH3-11, VH3-15, VH-3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51; and

~~iv)~~ v) a fourth population of ~~fourth~~ oligonucleotides encoding:

A) three heavy chain CDRs, wherein the three heavy chain CDRs comprise at least one heavy chain CDR altered with respect to said heavy chain donor CDRs ~~first heavy chain CDRs, wherein said first heavy chain CDRs comprise donor CDR variants, wherein said donor CDR variants comprise a different amino acid at only one, two, three or four positions compared to one of said three heavy chain donor CDRs, and~~

~~B) second heavy chain CDRs, wherein said second heavy chain CDRs encode each of said three heavy chain donor CDRs;~~

vi) wherein said third population of oligonucleotides and said fourth population of oligonucleotides overlap to encode a population of heavy chain variable regions comprising said unvaried human germline heavy chain framework regions and said heavy chain CDRs,

b) mixing said first population of ~~first~~ oligonucleotides and said second population of ~~second~~ oligonucleotides such that a fifth population of ~~fifth~~ oligonucleotides is generated, said fifth population encoding said population of light chain variable regions ~~encoding light chain variable regions is generated~~, wherein at least one of said light chain variable regions encoded by said population of fifth oligonucleotides comprises i) an unvaried human germline light chain framework, and ii) at least one altered light chain donor CDR ~~variant~~;

c) mixing said third population of ~~third~~ oligonucleotides and said fourth population of ~~fourth~~ overlapping oligonucleotides such that a sixth population of ~~sixth~~ oligonucleotides is generated said sixth population encoding said population of heavy chain variable regions ~~encoding heavy chain variable regions is generated~~, wherein at least one of said heavy chain variable regions encoded by said population of sixth oligonucleotides comprises; i) an unvaried human germline heavy chain framework, and ii) at least one altered heavy chain donor CDR ~~variant~~; and

d) expressing said fifth and sixth populations of oligonucleotides to produce combinations of heteromeric variable region binding fragments.

18. (original) The method of Claim 17, further comprising step e) identifying at least one heteromeric variable region having higher antigen binding affinity than said donor heteromeric variable region.

19. (currently amended) The method of Claim 17, wherein said unvaried human germline light chain framework regions comprise[[s]] FR1, FR2, FR3 and FR4 regions configured to hybridize to said light chain donor CDRs and said light chain donor CDR variants such that said population of fifth oligonucleotides encoding light chain variable regions is generated.

20. (currently amended) The method of Claim 17, wherein said unvaried human germline heavy chain framework regions comprise[[s]] FR1, FR2, FR3 and FR4 regions configured to hybridize to said heavy chain donor CDRs and said heavy chain donor CDR variants such that said population of ~~fifth~~ sixth oligonucleotides encoding heavy chain variable regions is generated.

21.(new) The method of Claim 17, wherein at least two light chain CDRs are altered with respect to said light chain donor CDRs.

22. (new) The method of Claim 17, wherein at least two heavy chain CDRs are altered with respect to said heavy chain donor CDRs.